

Comparison of clinical and morphological characteristics of *Staphylococcus aureus* endocarditis with endocarditis caused by other pathogens

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Objectives: To analyse clinical, echocardiographic, and prognostic characteristics of *Staphylococcus aureus* infective endocarditis (IE) compared with endocarditis caused by other pathogens.

Design: Cohort study.

Methods: 194 consecutive patients with definite IE according to the Duke criteria prospectively examined by transthoracic and transoesophageal echocardiography were enrolled. Patients without identified microorganisms were excluded. The *S aureus* IE group (n = 61) was compared with the group with IE caused by other pathogens (n = 133).

Results: Compared with IE caused by other pathogens, *S aureus* IE was characterised by severe co-morbidity, a shorter duration of symptoms before diagnosis, and a higher prevalence of right sided IE, cutaneous portal of entry, and history of renal failure. Severe sepsis, major neurological events, and multiple organ failure were more frequent during the acute phase in *S aureus* IE. In-hospital mortality (34% v 10%, p < 0.001) was higher in patients with *S aureus* IE and the 36 month actuarial survival rate was lower in *S aureus* IE than in IE caused by other pathogens (47% v 68%, p = 0.002). Multivariate analyses identified *S aureus* infection as a predictive factor for in-hospital mortality and for overall mortality.

Conclusions: *S aureus* IE compared with IE caused by other pathogens occurs in a more debilitated clinical setting and is characterised by a higher prevalence of severe sepsis, major neurological events, and multiple organ failure leading to higher mortality.

Staphylococcus aureus and streptococci are the main microorganisms responsible for infective endocarditis (IE).^{1,2} *S aureus* IE is a malignant disease, with a constantly increasing frequency estimated between 17–40% of cases in recent series.^{1–8} Few studies have been specifically devoted to *S aureus* IE,^{9–14} have not compared *S aureus* IE with IE caused by other microorganisms, and have not systematically used transoesophageal echocardiography (TOE). The objective of this single centre study was to analyse the clinical, echocardiographic, and prognostic characteristics of *S aureus* IE and to compare them with the characteristics of IE caused by other pathogens.

METHODS

Patients

Between January 1990 and December 2000, 243 consecutive patients with definite IE according to the Duke criteria^{15, 16} were referred to our echocardiographic laboratory. The Duke criteria were applied retrospectively to patients hospitalised before publication of the Duke criteria. All patients were examined by transthoracic echocardiography (TTE) and TOE. Of the 243 patients, 194 patients with a positive blood culture were prospectively enrolled. Patients without identified microorganisms (n = 49) were excluded. In 61 patients (25.2%) *S aureus* was isolated, 15 patients (6%) had *Staphylococcus epidermidis* IE, 85 patients (35%) had streptococcal IE, 21 patients (8.7%) had enterococcal IE, and 12 patients (4.9%) had IE caused by uncommon microorganisms. The results of blood cultures were provided by the bacteriology laboratories and comprised identification of bacteria and antibiotic susceptibility testing. Patients were divided into two groups according to the microorganisms isolated: *S aureus* IE group (n = 61) and other pathogens IE group (n = 133).

Clinical parameters

Age, sex, presence of co-morbidity (history of diabetes, cancer, haematological malignancy, cirrhosis, renal failure, dialysis, heart failure, or coronary artery disease), hypertension, valvar heart disease, valve prosthesis, cardiac surgery, and the presence of an intravascular device (venous catheter, pacemaker, or dialysis device) were analysed. A co-morbidity index taking into account the patient's age and history was calculated.¹⁷

The following acute clinical events present on admission or occurring during hospitalisation were recorded: heart failure, neurological event, peripheral embolism, severe sepsis, multiple organ failure, and hospitalisation in the intensive care unit. The duration of symptoms before admission (interval between the presumed onset of symptoms and the date of admission for IE) and the portal of entry of the infection were investigated. Embolic events were diagnosed based on clinical signs and data derived from a non-invasive procedure (cerebral and thoraco-abdominal computed tomography recorded in 70% of patients).¹⁸ A major neurological event was defined as the development of an ischaemic stroke with hemiplegia, haemorrhagic stroke, cerebral abscess, features of encephalopathy, or coma.¹⁹ A minor neurological event was defined as a transient ischaemic attack or cerebral embolic accident with no serious clinical signs.¹⁹ Severe sepsis was defined as a systemic inflammatory syndrome secondary to an infectious process leading to organ dysfunction or signs of hypoperfusion or hypotension.²⁰ Multiple organ failure was defined as dysfunction of at least two organs during hospitalisation for IE.

Echocardiography

Echocardiography was performed with a Hewlett Packard Sonos phased array (HP 1000, HP 2500 or HP 5500; Hewlett

Table 1 Comparison of clinical setting of *Staphylococcus aureus* infective endocarditis (IE) versus IE caused by other pathogens

Variable	<i>S aureus</i> (n = 61)	Other pathogens (n = 133)	p Value
Age (years)*	57 (16)	60 (14)	0.20
Men/women	42 (69%)/19 (31%)	98 (74%)/35 (26%)	0.48
Co-morbidity index >4	28 (46%)	44 (33%)	0.086
≥1 co-morbidities	37 (61%)	58 (44%)	0.027
≥2 co-morbidities	22 (36%)	28 (21%)	0.026
Hypertension	21 (34%)	47 (35%)	0.9
Diabetes	12 (20%)	16 (12%)	0.16
Cancer	11 (18%)	30 (23%)	0.47
Alcoholism	12 (20%)	23 (17%)	0.68
Cirrhosis	3 (5%)	7 (5.3%)	1
History of renal failure	18 (29%)	10 (7%)	<0.001
Dialysis	7 (11%)	2 (1.5%)	0.005
History of heart failure	6 (10%)	9 (7%)	0.45
History of coronary disease	5 (8%)	8 (6%)	0.57
Intravascular device	11 (17%)	14 (11%)	0.12

*Mean (SD).

Packard, Andover, Massachusetts, USA) ultrasound machine with a 2.5 MHz transthoracic transducer and a 5 MHz transoesophageal transducer. TTE was systematically completed by TOE. All echocardiographic studies were performed by standard techniques and by experienced echocardiographers during the acute phase of IE without any complications. The presence, size, and location of valvar vegetation or perivalvar abscess were evaluated. Standard definitions were used for vegetations, abscesses, and other cardiac infective lesions.^{15 21 22} All TOE recordings were reviewed by an experienced echocardiographer to measure in various planes the maximum length of vegetations¹⁸ and the maximum surface area of abscesses.²³ The mobility of vegetations was graded on a scale of 1 to 4 with severe mobility corresponding to grade 4.²⁴ Valvar regurgitation was quantified by Doppler echocardiography by standard method.²⁵

Follow up

Follow up data included surgical treatment and death occurring during hospitalisation or follow up. Early surgery was defined as surgery performed during hospitalisation for management of IE.^{5 26} In-hospital mortality was defined as death occurring during the hospitalisation for IE.^{5 26} Overall mortality refers to death occurring during hospitalisation and follow up. Late mortality excluded death occurring during hospitalisation. All patients completed follow up with a mean follow up duration of 30 months.

Statistical analysis

Data were statistically analysed with SPSS 9.0 software (SPSS Inc, Chicago, Illinois, USA). Quantitative variables were expressed as the mean (SD). The two groups were compared by Student's *t* test or χ^2 test. The cumulative probability of survival was estimated by the Kaplan-Meier actuarial method at one month intervals and reported as mean (SE) estimated survival. The log rank test was used to determine any significant differences. To evaluate the impact of *S aureus* IE on survival, multivariate models incorporating age, sex, co-morbidity index (taking the patient's age and history into account), usual prognostic factors (prosthetic valve, heart failure, major neurological events, renal failure, abscess, vegetation size), and early surgery were studied. A multivariate logistic regression model was used to determine in-hospital mortality and a Cox multivariate model for overall mortality. A probability value of *p* < 0.05 was considered significant.

RESULTS

Baseline characteristics

Of the 194 patients studied (140 men and 54 women, mean (SD) age 59 (15) years), 61 patients had *S aureus* IE and 133 patients had IE caused by other microorganisms. Twenty four per cent of patients of our series were referred from another hospital. IE affected a native valve in 89% of patients and a valve prosthesis in 11% of patients (six mechanical prosthesis, 15 biological prosthesis). A vegetation was visualised in 98% of cases and a perivalvar abscess in 22%. Early surgery was performed on 37% of patients (33% of patients with *S aureus* IE and 39% of patients in IE caused by other pathogens, *p* = 0.33). The indications for early surgery were heart failure in 18 patients (25%), embolic risk in 16 (22%), uncontrolled infection in 15 (21%), severe regurgitation in six (8%), abscess in three (4%), and multiple indications in 14 (19%). In the 72 patients who underwent early surgery, 24 had mechanical valves, 22 had biological valves, 14 had mitral valve or tricuspid valve repair, six had pacemaker line extraction, four had multiple valve surgery, one had a homograft, and one had aortic valve vegetectomy.

Table 2 Comparison of patients' clinical characteristics during hospitalisation for *S aureus* IE versus IE caused by other pathogens

Variable	<i>S aureus</i> (n = 61)	Other pathogens (n = 133)	p Value
Native valve disease	55 (90%)	118 (89%)	0.76
Prosthetic valve	6 (10%)	15 (11%)	0.76
Aortic IE	22 (36%)	57 (43%)	0.37
Mitral IE	28 (46%)	46 (35%)	0.13
Right sided IE	11 (18%)	8 (6%)	0.009
Multiple valve IE	0 (0%)	24 (18%)	<0.001
Duration of symptoms (days)*	15 (19)	42 (51)	<0.001
GI portal of entry	0 (0%)	35 (26%)	<0.001
Cutaneous portal of entry	29 (47%)	11 (8%)	<0.001
Heart failure	19 (31%)	50 (38%)	0.38
Severe sepsis	24 (39%)	8 (6%)	<0.001
Stay in intensive care unit	27 (44%)	14 (10%)	<0.001
Embolic event	29 (47%)	56 (42%)	0.47
Minor neurological event	10 (16%)	26 (19%)	0.60
Major neurological event	11 (18%)	11 (8%)	0.04
Multiple organ failure	18 (29%)	14 (10%)	0.001
Early surgery	20 (33%)	52 (39%)	0.39
In-hospital mortality	21 (34%)	13 (10%)	<0.001

*Mean (SD).
GI, gastrointestinal.

Table 3 Comparison of echocardiographic characteristics of *S aureus* IE versus IE caused by other pathogens

Variable	<i>S aureus</i> (n = 61)	Other pathogens (n = 133)	p Value
Length of vegetation (mm)*	1.4 (8)	1.2 (7)	0.21
Severe mobile vegetation	18 (38%)	38 (30%)	0.30
Presence of abscess	14 (23%)	23 (14%)	0.35
Abscess area (cm ²)*	1.5 (1.6)	2.2 (2.3)	0.36
Severe regurgitation	17 (30%)	62 (47%)	0.014

*Mean (SD).

The mean duration of antibiotic treatment before surgery was 10 (8) days in the *S aureus* IE group and 15 (16) days in other pathogens group ($p = 0.30$).

Comparison of clinical characteristics

Tables 1 and 2 show the results of univariate analysis comparing clinical setting and clinical characteristics during hospitalisation of *S aureus* IE versus IE caused by other pathogens.

Mean age, sex ratio, prevalence of history of hypertension, history of heart failure, history of coronary disease, cancer, alcoholism, cirrhosis, frequency of prosthetic valve IE, aortic valve IE, acute heart failure, embolic event, minor neurological event, and of early surgery were comparable between the two groups (tables 1 and 2). Compared with IE caused by other pathogens, *S aureus* IE was characterised by severe comorbidity ($p = 0.026$), a shorter mean duration of symptoms before admission ($p < 0.001$), a higher prevalence of history of renal failure ($p < 0.001$) and dialysis ($p = 0.005$), right sided IE ($p = 0.009$), a cutaneous portal of entry ($p < 0.001$), severe sepsis ($p < 0.001$), admission to the intensive care unit ($p < 0.001$), multiple organ failure ($p = 0.001$), and major neurological events ($p = 0.04$) (tables 1 and 2).

Echocardiographic findings

Table 3 compares echocardiographic characteristics. The presence and size of abscess, mean vegetation size, and

Table 4 Comparison of clinical complications among patients who died in hospital with *S aureus* IE versus IE caused by other pathogens

Variable	<i>S aureus</i> (n = 21)	Other pathogens (n = 13)	p Value
Age (years)*	62 (12)	57 (14)	0.29
Severe sepsis	16 (76%)	3 (23%)	0.004
Major neurological event	7 (33%)	4 (31%)	1
Renal failure	9 (43%)	4 (31%)	0.7
Heart failure	11 (52%)	9 (69%)	0.33
Multiple organ failure	14 (67%)	6 (46%)	0.28

*Mean (SD).

severe mobile vegetations were comparable in the two groups. Severe valvar regurgitation and multiple valve endocarditis were less frequent in the *S aureus* IE group.

Mortality

In-hospital mortality was 17% in the total population. Compared with IE caused by other pathogens, the in-hospital mortality rate was higher in patients with *S aureus* IE (34% *v* 10%, $p < 0.001$). Table 4 reports the clinical complications of patients who died in hospital. Severe sepsis was more frequent in patients who died during the hospital phase of IE in the *S aureus* IE group. Among the 61 patients with *S aureus* IE, 21 died during the acute phase of IE. The causes of death in the *S aureus* IE group were multiorgan failure in 12 patients, neurological event in two, sudden death in three, heart failure in one, operative death in two, and tamponade in one. The causes of death among the 13 patients who died in the other pathogens group during the acute phase of IE were multiorgan failure in five patients, neurological event in two, sudden death in three, and operative death in three. The mean duration of antibiotic treatment before death was 22 (19) days in the *S aureus* IE group versus 22 (18) days ($p = 0.95$).

The overall 36 month mortality rate was 35%. By multivariate analyses *S aureus* infection was identified as a powerful predictive factor for in-hospital mortality and for overall mortality (tables 5 and 6). The 36 month actuarial

Table 5 Impact of *S aureus* infection on in-hospital mortality: results of logistic regression analysis models

Model	OR	95% CI	p Value
Age and sex adjusted models			
Age	1	0.98 to 1	0.47
Sex	0.5	0.2 to 1.3	0.20
Staphylococcus IE	5.2	2.3 to 11.5	<0.001
Sex, C index, and usual prognosis variables adjusted models			
Sex	0.4	0.13 to 1.2	0.13
C Index	1.2	0.98 to 1.5	0.06
Prosthetic valve	3.1	0.53 to 18.8	0.20
Major neurological event	9.1	2.6 to 31	0.0004
Heart failure	4.9	1.7 to 13.7	0.0021
Abscess	1.2	0.35 to 4.1	0.75
Vegetation size	1.03	0.97 to 1.1	0.20
Staphylococcus IE	6.4	2.4 to 16.6	0.0001
Age, sex, usual prognosis factors, and early surgery adjusted models			
Age	1	0.96 to 1.04	0.87
Sex	0.4	0.11 to 1.44	0.16
Early surgery	0.51	0.16 to 1.56	0.24
Prosthetic valve	3.86	0.59 to 25	0.15
Renal failure	6.3	1.9 to 20.4	0.0022
Abscess	1.6	0.45 to 5.66	0.46
Vegetation size	1.04	0.97 to 1.12	0.17
Major neurological event	10.4	2.7 to 39	0.0005
Heart failure	5.3	1.8 to 15	0.0023
Staphylococcus IE	4.7	1.7 to 13.3	0.0029

C index, co-morbidity (including age and renal failure); CI, confidence interval; OR, odds ratio.

Table 6 Impact of *S aureus* infection on overall mortality: results of Cox proportional hazard regression analysis models

Model	Hazard ratio for death	95% CI	p Value
Age and sex adjusted models			
Age	1.02	1 to 1.03	0.022
Female sex	0.7	0.45 to 1.3	0.40
Staphylococcus IE	2.2	1.3 to 3.6	0.001
Sex, C index, and usual prognosis variables adjusted models			
Sex	0.56	0.32 to 0.97	0.04
C index	1.3	1.17 to 1.44	<0.0001
Prosthetic valve	2.5	1.17 to 5.3	0.017
Major neurological event	3.2	1.7 to 6.2	0.0003
Heart failure	1.8	1.12 to 3.04	0.015
Abscess	1.03	0.54 to 1.9	0.92
Vegetation size	0.99	0.96 to 1.03	0.99
Staphylococcus IE	1.9	1.2 to 3.2	0.0054
Age, sex, early surgery, and usual prognosis variables adjusted models			
Age	1	0.99 to 1.02	0.31
Sex	0.68	0.39 to 1.20	0.19
Surgery	0.53	0.29 to 0.95	0.035
Prosthetic valve	2.5	1.22 to 5.43	0.012
Renal failure	2.1	1.18 to 4.04	0.012
Abscess	1.05	0.54 to 2.02	0.87
Vegetation size	1.01	0.97 to 1.04	0.48
Major neurological event	3.37	1.08 to 6.3	0.0001
Heart failure	2.26	1.36 to 3.77	0.0016
Staphylococcus IE	1.8	3.1	0.017

overall survival rate was significantly lower in the *S aureus* IE group than in the group with IE caused by other pathogens (47% v 68%, $p = 0.002$) (fig 1).

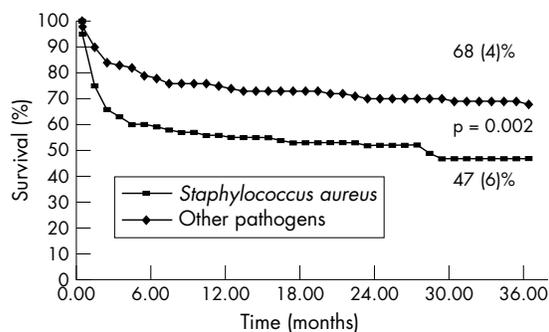
Thirty four of the 160 survivors after hospitalisation died after discharge during the 36 month follow up. The causes of late death were heart failure in seven patients, neurological event in four, cancers in seven, sudden death in two, myocardial infarction in one, operative death in one patient who underwent cardiac surgery after discharge at four months, and unknown in 12. The 36 month late survival rate after discharge was similar in the two groups (72% v 75%, $p = 0.95$; fig 2).

DISCUSSION

Our study of 194 patients with definite IE according to the Duke criteria^{15 16} shows that *S aureus* IE compared with IE caused by other pathogens is characterised by a shorter duration of symptoms before diagnosis and by a higher prevalence of co-morbidity, history of renal failure, right sided IE, cutaneous portal of entry, severe sepsis, major

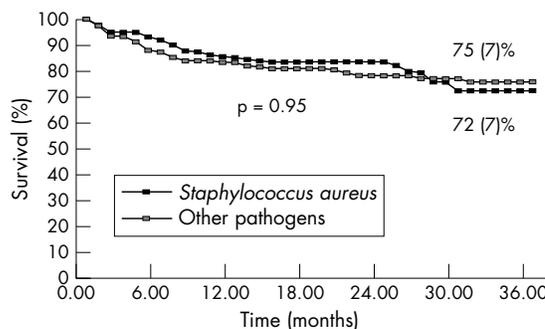
neurological events, and multiple organ failure. *S aureus* IE is more severe in terms of morbidity and mortality. To our knowledge, clinical and morphological characteristics have not been compared between *S aureus* IE and IE caused by other pathogens in terms of the Duke criteria.

S aureus IE has been reported with increasing frequency during the past decades^{3 6 13} and has emerged as a dominant cause of IE.^{6 27} In our study *S aureus* was responsible for 25% of all cases of IE. *S aureus* IE usually occurs in a debilitated clinical setting: chronic renal failure, haemodialysis, diabetes, alcoholism, cancer, haematological malignancy, immunodepression, and drug addiction.^{6 12 28 29} In our study, severe co-morbidity was associated with *S aureus* IE. The association between haemodialysis, renal failure, and *S aureus* IE was confirmed in our study. This susceptibility may be caused in part by an underlying disease and its treatment (immunosuppression, intravenous catheter). *S aureus* is a bacterium that easily adheres to inert structures. Intravascular device associated *S aureus* IE has recently been recognised as an emerging problem by other investigators.^{13 30} In our series, the presumed source of infection was an intravascular device in



Other pathogens IE	133	93	78	71	65	59	54
<i>S aureus</i> IE	61	33	30	25	24	19	17

Figure 1 Kaplan-Meier overall survival curves of patients with *Staphylococcus aureus* infective endocarditis (IE) and IE caused by other pathogens. The survival of patients with *S aureus* IE is lower (47%) than that of patients with IE caused by other pathogens (68%, $p = 0.002$).



Other pathogens IE	120	93	78	71	65	59	54
<i>S aureus</i> IE	40	33	30	25	24	19	17

Figure 2 Kaplan-Meier late survival curves of patients with *S aureus* IE and IE caused by other pathogens. Late survival was similar in both groups (*S aureus* IE, 72%; other pathogens, 75%; $p = 0.95$).

17% of patients with *S aureus* IE.²⁹ Right sided IE was more frequent in the *S aureus* IE group.^{1 13} Not surprisingly, the cutaneous portal of entry was identified as a major source of infection in the *S aureus* IE group in our study. Only three patients in our study had a history of injecting drug use.

S aureus is a malignant disease known to be responsible for severe sepsis.^{31 32} Accordingly, admission to the intensive care unit, development of severe sepsis, and multiple organ failure were significantly more frequent in the *S aureus* IE group in our study. This virulence has been ascribed to a variety of complex factors, which include its capsule and cell wall, the production of extracellular enzymes and toxins that promote tissue invasion, its capacity to persist intracellularly in phagocytes, and its potential to acquire resistance to antimicrobials. Clinical signs of *S aureus* IE appear and evolve rapidly, leading to hospital admission^{3 4 9 14} as illustrated by the shorter mean duration of symptoms in the *S aureus* IE group in our study. Neurological complications are sometimes the first presenting signs of IE. Symptoms may range from simple confusion to unexplained coma.^{19 33} Previous series have noted a high incidence of neurological events in *S aureus* IE.^{19 34 35} Accordingly, a high frequency of 18% major neurological events in the *S aureus* IE group compared with 8% in IE caused by other pathogens was observed in our series. Only 11% of embolic events occurred after initiation of antibiotics. Because not all patients underwent cerebral and thoraco-abdominal computed tomography, the true incidence of embolic events in the current study may have been underestimated. The frequency of heart failure, one of the main complications of IE, was comparable in the two groups. Surgery was performed according to established guidelines, predominantly in the presence of a complication such as recurrent embolism, heart failure, or evidence of perivalvular extension.^{36 37} Because of the virulence of *S aureus* and the severity of the clinical features, some authors recommend aggressive management with very broad indications for early surgery performed in 33% of cases in the current series.^{3 38} However, surgery in the *S aureus* group is sometimes not performed because of a prohibitive operative risk related to the debilitated clinical setting associated with extremely severe clinical features and multiorgan failure (six patients in our series). In our study, as in other series reported in the literature,^{1 39-41} early surgery defined as surgery performed during hospitalisation for management of IE^{5 26} was also frequent in the group with IE caused by other pathogens. The benefit of early surgery in patients with *S aureus* IE was not addressed in the current study, which has the disadvantages of observational studies of consecutive patients where the decision to operate or not was not randomised but based on the clinical judgement of the physician or surgical team. Thus, further studies are needed to evaluate whether earlier surgical intervention for selected patients will improve the outcome of *S aureus* IE.³⁷

S aureus IE is associated with high morbidity and mortality. *S aureus* IE compared with IE caused by other pathogens occurs in a more debilitated clinical setting. The prognosis of *S aureus* IE is therefore very serious, with a more severe prognosis than with IE caused by other pathogens and with a high in-hospital mortality of 34% in our series, which ranges between 30–46% according to various authors,^{1-3 31 42} even reaching 71% in a study published in 1986.⁹ The present study showed that in IE, independent of age, sex, co-morbidity index or usual prognostic factors, *S aureus* infection causes an excess risk of in-hospital mortality and of overall mortality. Because *S aureus* right sided IE is a different disease, we performed a separate prognostic multivariate analysis excluding *S aureus* right sided IE. We obtained similar results to the analysis including all patients. Patients with *S aureus* prosthetic IE are a very high risk subgroup. In the current

study we had only six patients with a prosthetic valve in the *S aureus* IE group. Therefore, we could not specifically analyse *S aureus* prosthetic IE and compare it with non-*S aureus* IE. We cannot exclude the possibility that our patients may constitute a selected cohort from a referral centre with more severe illness than the average population with IE. Thus, the differences in mortality and morbidity may to some extent be a result of referral bias.

The excess mortality associated with *S aureus* IE in the current study, essentially related to the severity of sepsis and the particularly high risk clinical setting, mainly occurs during the hospital phase as indicated by actuarial survival curves, which tend to become parallel in the two groups after discharge from hospital (fig 1). Accordingly, *S aureus* infection was not a predictive factor of late mortality. Rapid management is therefore essential with a need for early surgery in selected patients.^{3 36 38}

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IMAGES IN CARDIOLOGY

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Spontaneous stent-edge spasm in a patient with myocardial infarction

A 57 year old Japanese man who had no history of vasospastic angina was admitted because of acute myocardial infarction complicated by ventricular fibrillation. He was resuscitated by cardioversion. Coronary angiography revealed a 90% stenosis in the proximal portion of the left anterior descending artery (LAD). A coronary stent (Zeta stent 3.5–28 mm) was deployed in the proximal LAD lesion. Although he had been asymptomatic, follow up angiography was performed four months later. In the first angiogram of the LAD, luminal narrowing at the stent distal edge was noted (panel A: white arrows denote the stent-edge spasm site). We considered the following two possibilities: stent-edge restenosis had occurred or there was spontaneous stent-edge spasm. Ergonovine was injected into the LAD in incremental doses of 10 µg (panel B) and 20 µg (panel C) over four minutes. After the injection of ergonovine, luminal narrowing at the distal edge of the stent increased (panel B) and severe narrowing with filling delay was observed (panel C). The spasm resolved with intracoronary administration of 3 mg of isosorbide dinitrate and the luminal narrowing at the stent distal edge disappeared (panel D). After follow up angiography, treatment with a calcium channel antagonist was started. Although spontaneous stent-edge spasm is rare, we should not neglect this phenomenon.

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